Urticarial lesions: If not urticaria, what else? The differential diagnosis of urticaria

Part I. Cutaneous diseases

Anna Peroni, MD,[a,c] Chiara Colato, MD,[b] Donatella Schena, MD,[a] and Giampiero Girolomoni, MD[a]
Verona, Italy

Acute urticaria is self-limiting, and a cause can be identified in many patients. Chronic urticaria is a long lasting disease, and patients are commonly examined for an autoimmune origin and for associated diseases. Although the diagnosis of urticaria is straightforward in most patients, it may pose some difficulties at times and it may require a careful differential diagnosis with a number of conditions. Urticarial syndromes comprise both cutaneous and systemic disorders. Part I of this two-part series focuses on the clinical and histologic features that characterize common urticaria and on the cutaneous diseases that may manifest with urticarial lesions and must be considered in the differential diagnosis. (J Am Acad Dermatol 2010;62:541-55.)

Learning objectives: After completing the learning activity, participants should be able to distinguish between the typical wheals of urticaria and urticarial lesions suggesting other diagnoses and to assess patients with urticarial lesions in order to exclude or confirm other cutaneous diseases.

Key words: bullous pemphigoid; drug eruption; insect bite reactions; urticaria; urticarial dermatitis; urticaria pigmentosa.

Urticaria is a common disorder with a complex and not well understood physiopathology. The main effector cell is the cutaneous mast cell, which can degranulate in response to many different causes (eg, drugs, chemical compounds, autoantibodies, complement factors, or proteases) and can release histamine and other mediators that are eventually responsible for wheal formation. Other than vasodilatation and dermal edema, urticaria is associated with a scanty to moderate perivascular infiltrate of T cells, monocytes, neutrophils, and eosinophils.[1,2] Spontaneous urticaria is classically distinguished into an acute form, when lasting less than 6 weeks, or into a chronic form, when lasting longer than 6 weeks.[3] Acute urticaria patients are usually handled by the general practitioner or in an emergency room setting. In contrast, patients with chronic urticaria are commonly referred to a specialist—often a dermatologist or an allergist—to confirm diagnosis, to search for possible causes or disease association, and to start a therapy. Although the diagnosis of urticaria is straightforward in most patients, it may pose some difficulties at times. Urticarial syndromes include both cutaneous and systemic disorders. The objectives of this article are to discuss the major clinical features of cutaneous conditions resembling urticaria briefly and to discuss the differential diagnosis of urticaria. Differential diagnosis with systemic conditions is the focus of part II of this series.

Abbreviations used:

FcεRIα:	high affinity IgE-receptor
IGD:	interstitial granulomatous dermatitis
NEH:	neutrophilic eccrine hidradenitis
NSAID:	nonsteroidal antiinflammatory drug
PUPPP:	pruritic urticarial papules and plaques of pregnancy

From the Department of Biomedical and Surgical Sciences,[a] Section of Dermatology and Venereology and the Departments of Pathology, Sections of Pathology[b] and Immunology,[c] University of Verona, Italy.

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Correspondence to: Giampiero Girolomoni, MD, Clinica Dermatologica, Università di Verona, Piazzale A. Stefani 1, 37126 Verona, Italy. E-mail: giampiero.girolomoni@univr.it.

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ACUTE AND CHRONIC URTICARIA

Key points

- **Acute urticaria is common in both children and adults. It is a self-limiting condition**

commonly related to infections, food, or drugs

- **Chronic urticaria mainly affects adults and is rare in children. Often, no obvious causes can be identified**
- **Typical wheals of spontaneous urticaria appear as circumscribed cutaneous reliefs, elastic in consistency and erythematous or pale in color; they may have variable dimensions and shapes, a random distribution on the body surface, and last no more than 24 to 36 hours with no residual skin changes**

CAPSULE SUMMARY

- Common skin diseases that can manifest with wheal-like lesions include urticarial dermatitis, contact dermatitis, arthropod bite reaction, drug eruptions, urticaria pigmentosa, subepidermal autoimmune bullous diseases, and pruritic urticarial papules and plaques of pregnancy.
- Rare urticarial skin diseases include autoimmune progesterone/estrogen dermatitis, interstitial granulomatous dermatitis, eosinophilic cellulitis (Wells syndrome), neutrophilic eccrine hidradenitis, and urticaria-like follicular mucinosis.
- Each of the above may manifest with skin lesions other than wheals (eg, scaling and blistering). Lesions are more likely to have a bilateral and symmetrical distribution. Individual lesions have a long duration, and their resolution may leave marks, such as hyperpigmentation.
- Clinicopathologic correlation is often essential to establish the correct diagnosis.

Acute urticaria is common in both children and adults, with a lifetime prevalence of about 15% to 20% in the general population,[4] and tends to be self-limited, with a complete resolution within 3 weeks in more than 90% of cases.[5] The most commonly identified causes of acute urticaria are infections (about 40% of cases), particularly viral infections of the upper respiratory tract, followed by drugs, food (mainly seafood and fruit), and insect bites.[4,5] Drugs and foods can elicit acute urticaria either or both as allergens (eg, penicillin) and as pseudoallergens (eg, nonsteroidal antiinflammatory drugs [NSAIDs] and opiates); the allergic reaction is caused by the presence of specific immunoglobulin E (IgE) antibodies that activate skin mast cells by cross-linking high affinity IgE receptors (FcϵRIα) when bound to the substance (eg, food and penicillins). The pseudoallergic reaction instead is related to a still undefined direct action of the substance on skin mast cells (eg, opiates) or to the interference of drugs (eg, aspirin and other NSAIDs) which inhibit cyclooxygenase (COX) 1 and COX 2 with arachidonic acid metabolism, leading to an increased synthesis of cysteinyl leukotrienes, which in turn induces vasodilatation and edema.[6,7] Moreover, in some patients it is the combination of the viral infections (increasing mast cell reactivity) and drug intake that elicits urticaria.[4] The prevalence of different etiologies varies among different age groups; for children, the main etiologies are infections and food, whereas for adults medications are more frequent.[8] The cause of acute urticaria remains unclear in more than half of the patients. The primary concern with patients presenting with acute urticaria is to rule out the diagnosis of anaphylaxis and then provide adequate treatment to relieve severe pruritus. In addition to the skin (with urticaria or diffuse erythema), anaphylaxis involves the cardiovascular system and the respiratory and the gastrointestinal tracts. The reaction is typically sudden, but prolonged and biphasic forms exist. The main causes for anaphylactic reactions are hymenoptera venom, food, and drugs.[9,10] The demonstration of an increase of tryptase serum concentration can be very helpful in confirming the diagnosis,[9] but in most centers the results are only available days later, too late to be of immediate help.

Chronic urticaria has a prevalence of 0.5% to 3% in the general population, is rare in children, and usually persists for months or years.[11] Chronic urticaria has no obvious cause, although some factors (eg, drugs, infections, emotional stress, and food) can serve as eliciting stimuli. In some patients, there is evidence that chronic urticaria has an autoimmune origin caused by the presence of autoantibodies to FcϵRIα or to IgE itself.[2,12] The disease often has a deep impact on the patient's quality of life, because severe itch and cutaneous lesions interfere with sleep and with work and leisure activities.[13] Physical urticaria includes a heterogeneous group of conditions elicited by thermal changes, ultraviolet light, skin pressure, or rubbing.[14-17]

A clear distinction between acute and chronic urticaria cannot be made in the very early phases of the disease. For this reason, the differential diagnosis of urticaria in general and not that of acute or chronic urticaria will be discussed. Moreover, in clinical practice it is essential to suspect a disease other than urticaria during the initial patient evaluation. The diagnosis of urticaria is primarily clinical

Table I. Main features distinguishing urticaria from cutaneous diseases presenting with urticarial lesions

Common urticaria	Urticarial lesions (one or more of the following)
Only typical wheals:	Atypical "wheals":
Erythematous edematous lesions	Infiltrated plaques
Transient (<24-36 hrs)	Persistent (>24-36 hrs)
Asymmetric distribution	Symmetric distribution
Resolution without signs	Resolution with signs (hypo/hyperpigmentation or scarring)
No other associated elementary lesions (papules, vesicles, purpura, crusts, etc)	Other associated elementary lesions (papules, vesicles, scaling, crusts, etc)
Pruritic	Pruritic
Possibly associated with angioedema	Usually not associated with angioedema

(Table I). Indeed, all of the forms of urticaria emerge with a similar and unvarying picture, independently of the type and the etiology. The only primary skin lesion is a wheal, which is determined by a transient edema of the papillary dermis and which appears as a circumscribed cutaneous elevation with elastic consistency, pink or pale in color, and a variable erythematous surrounding flare (Fig 1, *A*). The dimension of the wheal may range from a few millimeters to several centimeters; their number can also vary, being few or numerous or covering virtually the entire body surface area. It is important to note that their distribution on the body surface is usually random and asymmetric, although in chronic urticaria wheals tend to appear in the same areas in a given patient. Individual wheals last no longer than 24 to 36 hours, and the lesions disappear without leaving skin marks. Wheals are typically pruritic or, in rare instances, are associated with a burning sensation. No other symptoms (eg, fever, arthralgia, or muscular pain) are present. In some instances, lesions can be absent at the time of consultation; in these cases, the patient's own photographs of the lesions can be useful. Upon histologic examination, wheals of common urticaria show some dermal edema and mild dilatation of dermal blood vessels, without signs of wall damage or leukocytoclasia, and a sparse perivascular infiltrate composed of macrophages, lymphocytes, and granulocytes, both eosinophils and neutrophils (Fig 1, *B*).[3] The predominance of lymphocytes or neutrophils may be relevant from a therapeutic point of view. Patients with a neutrophil dominant infiltrate may not respond to antihistamines alone and may require colchicine, dapsone, or a short course of steroids to achieve disease control.[18] Only small differences, if any, exist histologically between autoimmune and idiopathic urticaria; in particular, eosinophil activation appears to occur later or to be more persistent in patients without anti-FcϵRIα antibodies.[19] In about 40% of patients, urticaria is associated with angioedema, which is determined by transient swelling of the reticular dermis and/or subcutaneous tissue. Therefore, angioedema should not be considered a separate entity, but instead is better interpreted in the majority of cases as a clinical variant of an urticarial lesion determined by analogous pathogenetic mechanisms at a different skin depth. Angioedema typically appears as a cutaneous or mucous swelling with undetermined borders; it is pale or skin-colored, and it is often associated with pain or tenderness rather than pruritus. It heals more slowly than wheals, within up to 72 hours. Angioedema occurs more often on the face, especially on the lips and eyelids, and on the extremities and the genital area.

Generally, no laboratory investigations are needed in patients with acute urticaria. The evaluation of plasma levels of some inflammatory markers (C-reactive protein and interleukin-6) can be useful in identifying patients who are likely to be resistant to antihistamine therapy alone and therefore need systemic steroids to achieve disease control.[20] Evaluation of specific IgE by either skin or laboratory testing is indicated if strongly suggested by the patient's history or when urticaria is associated with an anaphylactic reaction.[4,21] In chronic urticaria, a reduced panel of laboratory examinations may be indicated, including full differential blood count, erythrocyte sedimentation rate, C-reactive protein, complement fractions, protein electrophoresis, and antinuclear antibodies.[3,22-24] Indeed, these tests may be altered during urticarial vasculitis, which is among the most important differential diagnoses of urticaria. Because autoimmune thyroiditis is more common in patients with chronic urticaria, antithyroperoxidase antibodies and thyroid function tests may be abnormal.[25] Many methods exist to detect anti-FcϵRIα antibodies, but unfortunately they are not standard and are not routinely available everywhere.[2,26] The substitute value of the autologous serum or plasma skin test for confirming autoimmune urticaria is still debated.[3,22,27] Specific eliciting tests can be used for physical urticarias.[2]

An important issue regarding patients with urticaria is to be confident that it is in fact urticaria. There are several conditions that may present with urticaria-like skin lesions. Urticarial syndromes are extremely heterogeneous but can be differentiated into

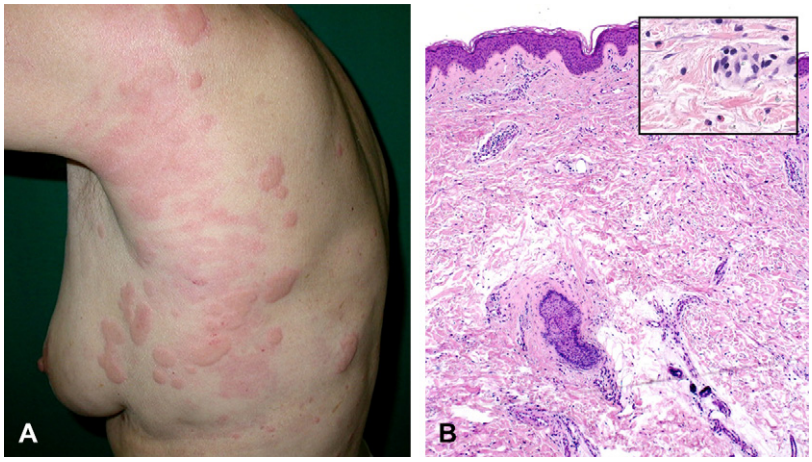

Fig 1. Ordinary urticaria. **A**, Erythematous wheals in different phases of development with no residual hyperpigmentation. **B**, Moderate dermal edema, dilation of dermal blood vessels, and a sparse perivascular infiltrate composed of macrophages, lymphocytes and granulocytes, both eosinophils and neutrophils. (Hematoxylin–eosin stain; original magnifications: ×100; *inset*, ×250.)

Table II. Principal cutaneous diseases that can manifest with urticarial lesions

Common
Urticarial dermatitis
Contact dermatitis (irritant or allergic)
Arthropod bite reactions
Exanthematous drug eruption
Mastocytosis (children)
Autoimmune bullous diseases
Subepidermal—bullous pemphigoid, gestational pemphigoid, linear IgA dermatosis, epidermolysis bullosa acquisita, and dermatitis herpetiformis of Duhring
Intraepidermal—pemphigus herpetiformis
Pruritic urticarial papules and plaques of pregnancy
Small-vessel vasculitis (urticarial vasculitis)
Rare
Autoimmune progesterone/estrogen dermatitis
Interstitial granulomatous dermatitis
Eosinophilic cellulitis (Wells syndrome)
Neutrophilic eccrine hidradenitis
Urticaria-like follicular mucinosis

cutaneous (Table II) and systemic diseases (as discussed in part II of this series). Cutaneous urticarial syndromes can be further distinguished as common and rare disorders.

COMMON CUTANEOUS URTICARIAL SYNDROMES

Common urticarial syndromes include urticarial dermatitis, contact dermatitis, arthropod bite reactions, exanthematous drug reactions, mastocytosis, subepidermal autoimmune bullous diseases, and pruritic urticarial papules and plaques of pregnancy (PUPPP). Moreover, urticarial vasculitis is probably the most important differential diagnosis of urticaria. Urticarial vasculitis is a small-vessel vasculitis with predominant cutaneous expression, but urticarial vasculitis is often associated with systemic involvement. For this reason, it is described in the second article in this series, among the systemic urticarial syndromes.

Urticarial dermatitis

Key points

- **Urticarial dermatitis usually affects elderly patients**
- **Cutaneous manifestations are long lasting patches with an urticarial and in some areas an eczematous appearance, with a bilateral and symmetrical distribution on the trunk or proximal extremities. Lesions are intensely pruritic**
- **Histologic examination reveals a predominantly dermal eczematous reaction with papillary dermal edema and superficial perivascular lymphocytic infiltration with eosinophils and minimal epidermal spongiosis**

Urticarial dermatitis has recently emerged as a useful clinical/histologic term to describe patients with a peculiar, predominantly dermal hypersensitivity reaction pattern.[28,29] Patients are 60 years of age on average, and they present with a very itchy diffuse skin disease characterized by urticarial and eczematous (scaling) features with variable prevalence of one aspect over the other during the course of the

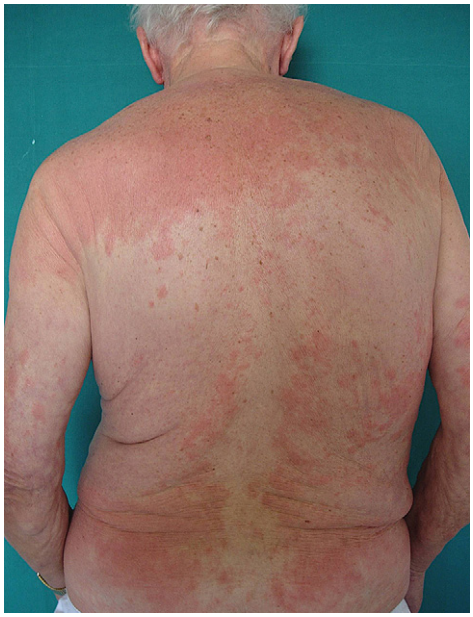

Fig 2. Urticarial dermatitis. Lesions are bilateral and symmetrically located on the trunk and proximal extremities.

disease (Fig 2 and Fig 3, *A*).[29] The lesions last for days to weeks and are bilateral and symmetrically located on the trunk and proximal extremities.[29,30] The lesions sometimes have a targetoid appearance with peripheral scaling, and excoriated erythematous papules may coexist. Lesions are intensely pruritic, and pruritus is unrelieved by treatment with antihistamines and topical corticosteroids.[29,30] The histologic picture is that of a predominantly dermal eczematous reaction with papillary dermal edema and superficial perivascular lymphocytic infiltration with eosinophils and minimal epidermal spongiosis (Fig 3, *B*).[29,31] The etiology remains elusive in most cases, but drugs are most likely implicated in many cases.[29,31] In general, a short course of medium dose systemic steroids is required to relieve pruritus and clear skin lesions. The disease can recur.

Contact dermatitis (irritant or allergic)

Key points

- **The clinical appearance is dominated by erythematous and edematous lesions**
- **It appears at the site of contact with substances**
- **Careful history plus patch testing and/or testing for specific IgE are able to confirm the allergic nature of the reaction**
- **A skin biopsy is rarely performed and reveals a mixed inflammatory infiltrate composed of lymphocytes, histiocytes, and a variable number of eosinophils. Epidermal spongiosis is present only in lesions with an eczematous appearance**

Contact dermatitis is one of the most common skin diseases, and it is caused by contact with irritants or allergens.[32-34] Irritant and allergic mechanisms can act in combination. Contact dermatitis presents mostly with an itchy eczematous reaction (acute or chronic), but in rare cases the reaction is mostly dermal, with minimal epidermal changes, and clinically it manifests with an erythematous and edematous (wheal-like) appearance. Contact urticaria is much less common and can also be distinguished in irritant (nonimmunologic) and allergic (immunologic) forms.

Nonimmunologic contact urticaria is the most frequent form. Causative agents include preservatives, fragrances, flavoring agents in foods, benzoic acid, sorbic acid, cinnamic acid, and cinnamic aldehyde; among metals, cobalt chloride can induce nonallergic contact urticaria. These agents can cause a reaction within 45 minutes after application on intact skin, and the reaction disappears within a few hours. Immunologic (IgE-mediated) contact urticaria occurs in few exposed individuals only after sensitization, and it is more likely in atopic patients. Substances capable of eliciting immunologic urticaria include natural latex, foods, topical medications, metals, chemicals, animal proteins, and textiles. The distinction between contact dermatitis and contact urticaria is not sharply defined. Indeed, some contact urticaria can be predominantly dermal eczematous reactions—as in urticarial dermatitis. On the other hand, the same substance can induce both types of reactions, and in some instances, true contact urticaria can be followed by a more typical eczematous reaction (eg, sorbic acid, cinnamic aldheyde, metals, latex, or exotic wood).[35] The diagnosis is usually made on a clinical basis, and a skin biopsy is rarely performed. An eczematous reaction shows the typical spongiotic dermatitis with mixed inflammatory infiltrate composed of lymphocytes, histiocytes, and a variable number of eosinophils. In chronic stages, acanthosis is prominent.[36,37] Urticarial lesions show only dermal changes and no epidermal spongiosis. For the identification of the specific causative allergen, epicutaneous patch tests and/or testing for specific IgE are essential. For food protein contact dermatitis, the open test can be helpful.

Arthropod bite reactions

Key points

- **Arthropod bite reactions usually appear as fixed pruritic papules, more often but not exclusively on exposed areas**

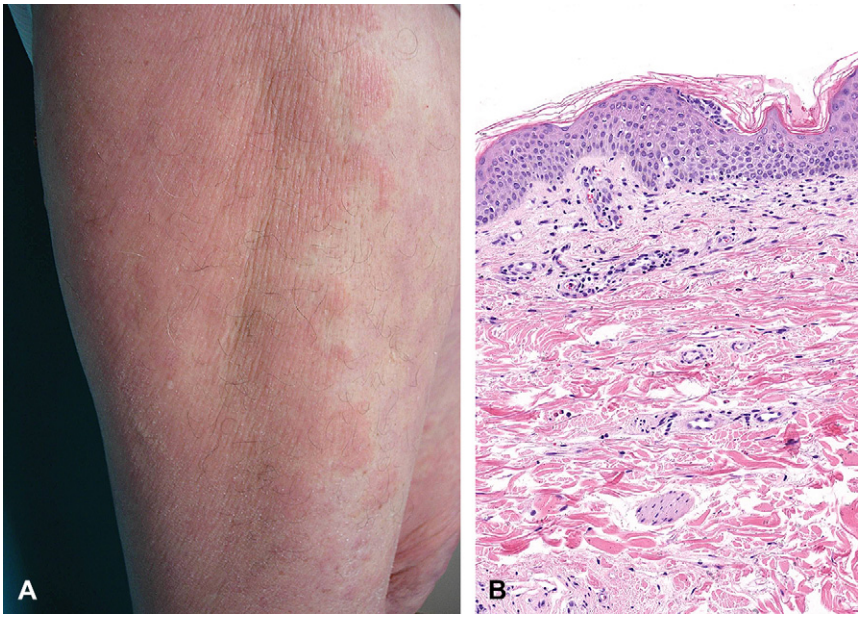

Fig 3. Urticarial dermatitis. **A**, Lesions have both urticarial and eczematous features (scaling). **B**, Minimal epidermal spongiosis, upper dermal edema, and perivascular mixed infiltration with the predominance of lymphocytes with some eosinophils. (Hematoxylin–eosin stain; original magnification: ×100.)

- **Papular urticaria appears as fixed, multiple, small erythematous wheals that evolve in pruritic brownish papules, sometimes capped by a vesicle, which eventually become excoriated**
- **Lesions more often appear during summer, and are persistent for days or months**
- **A histologic examination reveals mixed perivascular infiltrate, variable edema, and scattered interstitial eosinophils. The overlying epidermis shows spongiosis with variable exocytosis, vesicle formation, and excoriation**

Papular urticaria is interpreted as an allergic hypersensitivity reaction to arthropod bites; it is clinically characterized by multiple small erythematous wheals that subsequently evolve into pruritic brownish papules, sometimes capped by a vesicle, and which eventually become excoriated. Lesions more often appear during summer, are persistent for days or weeks (and more rarely for months), and they are usually predominant on exposed areas.[38] The histologic appearance is identical to that of persistent bite reactions: a mixed perivascular infiltrate, variable edema, and scattered interstitial eosinophils. The overlying epidermis shows some spongiosis with variable exocytosis, vesicle formation, and excoriation.[38] From a clinical point of view, papular urticaria should be differentiated from other conditions, such as papulovesicular polymorphous light eruption, varicella, prurigo simplex, Gianotti–Crosti syndrome, and miliaria rubra.[38] Immediate type localized insect bite reactions are typically urticarial. Lesions are commonly low in number and the patient is aware of the sting. In some instances, serious allergic systemic reactions occur (0.4-0.8% of children and 3% of adults).[39] Systemic reactions can be mild, manifesting as a generalized cutaneous response with urticaria and/or angioedema that subsides in a few days, or they can be severe and life-threatening (eg, anaphylaxis).[9,40]

Exanthematous drug eruptions

Key points

- **Erythematous fixed macules, papules, or wheal-like lesions appear mainly on the trunk with a bilateral and symmetric distribution. They have a tendency to confluence. Lesions disappear with a lamellar desquamation or leave some hyperpigmentation**
- **A history of drug intake must be present**
- **Low grade fever can be associated**
- **A histologic examination reveals mononuclear cell infiltrate around superficial dermal vessels with some eosinophils; scattered lymphocytes and apoptotic keratinocytes are present in the epidermis**

Maculopapular exanthema is the most common adverse drug reaction.[41] Skin lesions usually begin 4 to 14 days after starting a new medication—sometimes

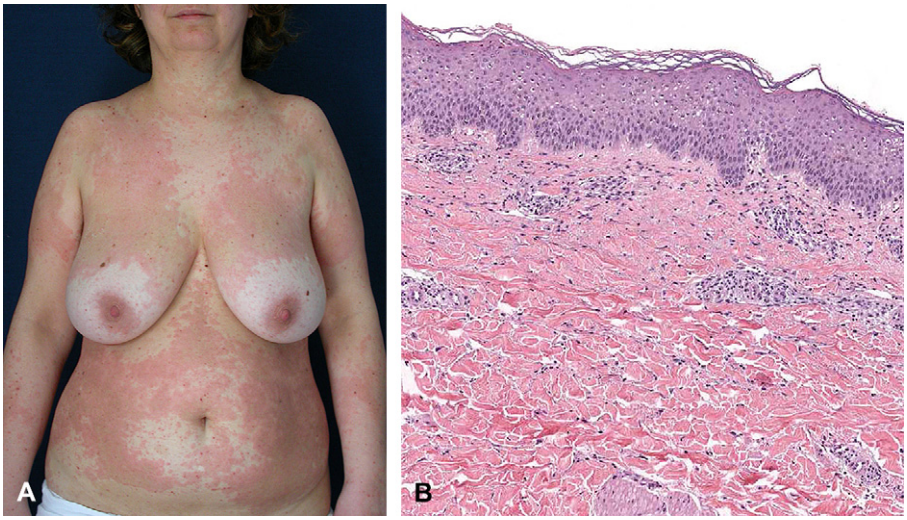

Fig 4. Urticarial drug eruption to omeprazole. **A**, Urticarial exanthematous lesions with a bilateral and symmetrical distribution and a tendency to confluence; note the residual hyperpigmentation. **B**, Dermal perivascular and interstitial infiltrate with eosinophils, edema of the papillary dermis, and rare apoptotic keratinocytes in the epidermis (*black arrow*). (Hematoxylin–eosin stain; original magnification: ×150.)

after the intake of that drug has ceased, or sooner in the case of rechallenge. They appear as erythematous macules that become slightly palpable, sometimes with a purpuric component. Lesions have a variable dimension (from pinpoint-sized papules to large flat macules), commonly with a bilateral and symmetric distribution. The eruption first involves the trunk and upper extremities, often starting from the axillae or the groin, and it progressively becomes confluent; mucous membranes are usually spared. Pruritus or low grade fever can be associated with the eruption. Lesions progressively fade, with a fine or lamellar desquamation within a few days or a few weeks.[41] In some instances, lesions closely resemble wheals, but they tend to become confluent, have a bilateral and symmetrical distribution, and leave a transient hyperpigmentation when they disappear (Fig 4, *A*). Histologically, they exhibit a mononuclear cell infiltrate around superficial dermal vessels with some eosinophils (Fig 4, *B*). The epidermis shows the presence of scattered lymphocytes and apoptotic keratinocytes. However, a skin biopsy is not always necessary to arrive at the diagnosis, and may also be unhelpful, because in mild cases the histologic changes are so subtle that they are nearly indistinguishable from normal skin.[41]

Cutaneous mastocytosis (urticaria pigmentosa)

Key points

- **Urticaria pigmentosa commonly presents with brownish maculopapular lesions. In children, urticarial lesions can be either spontaneous or induced by rubbing, heat, and sunlight exposure**
- **A positive Darier sign after skin rubbing is elicited in most cases**
- **Systemic involvement must be ruled out in adults**
- **Residual hyperpigmentation can persist after healing**
- **A cutaneous biopsy is recommended, but sometimes the histologic changes may not be prominent**

Mastocytosis is a heterogeneous disease characterized by the accumulation of mast cells in one or more organs—most frequently, the skin.[42] Mastocytosis is less rare than previously believed. In 65% of the cases, mastocytosis arises in children under 15 years of age, and in the remaining cases in young adults (20-40 years of age).[42] Pediatric cutaneous mastocytosis, unlike the adult form, is believed to represent a transient dysregulation of local mast cell growth factors. Indeed, c-kit mutations are different and less common in pediatric patients than in adults with mastocytosis.[43] Urticaria pigmentosa is the most common cutaneous manifestation of mastocytosis both in children and in adults, and it commonly manifests with brownish macules and papules, especially on the trunk and limbs. In children, however, lesions can present as an urticarial rash affecting the trunk, face, and limbs. Persistent urticarial lesions can be either spontaneous or induced by rubbing, heat, or sunlight (Fig 5, *A*).

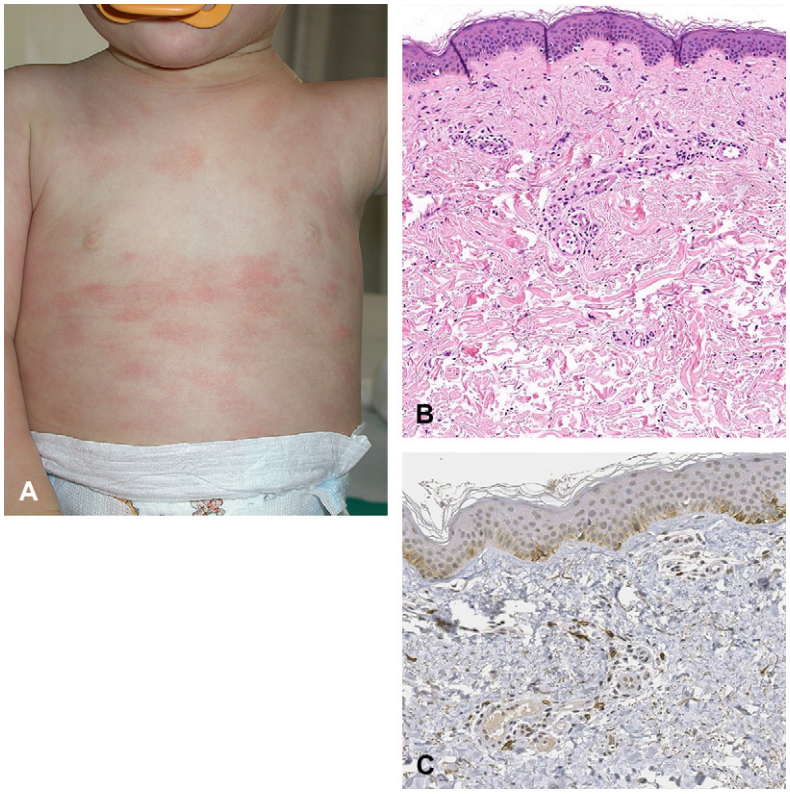

Fig 5. Urticaria pigmentosa in children. **A**, Urticarial erythematous fixed lesions on the face, trunk, and limbs. **B**, Increased number of perivascular mononuclear cells with ample cytoplasm **C**, Immnuohistochemical staining for c-Kit (CD117) shows a higher than normal number of positive cells. (**B**, Hematoxylin–eosin stain; original magnifications: **B**, ×100; C, ×150.)

Cutaneous mastocytosis lesions become more erythematous and edematous when rubbed (Darier sign), mimicking dermographism.[42,43] The number of lesions varies from a few to hundreds, but the extent of involvement does not predict systemic involvement. Flushing occurs in about 50% of patients, especially in children, who may also manifest recurrent syncope and anaphylaxis.[44] Blister formation may be associated, particularly in infants up to 2 years of age, and may even be the presenting symptom. The healing of blisters generally occurs without scarring, but residual hyperpigmentation may persist at the involved sites. Asymptomatic bone marrow involvement is very common in adults with urticaria pigmentosa, but it is very rare in children.[42] The diagnosis of cutaneous mastocytosis in children also requires a histologic confirmation, but the histologic changes may not be prominent enough to make a diagnosis if the clinical suspicion of mastocytosis is not put forward (Fig 5, *B*). Indeed, in some cases of urticaria pigmentosa, the number of dermal mast cells may not appear to be heightened, having the appearance of "seemingly normal skin." Mast cell count with c-kit staining is important in these cases (Fig 5, *C*). Serum tryptase is a marker of the total mast cell burden, and it is useful in the screening of patients for systemic involvement and in the follow-up.[42,45] The prognosis of mastocytosis strongly depends on the category of the disease and on the age of onset. The majority of pediatric cutaneous mastocytosis patients have an improvement of symptoms over time, with 50% having complete resolution by adolescence; conversely, most adult patients have a disease with a chronic indolent course and therefore have a normal life expectancy—spontaneous resolution is possible.[42,46] Patients who initially present with systemic mastocytosis may develop a slowly progressive disease, and 3% to 30% of patients can develop associated hematologic disorders.[46,47] A recent study[46] established that the presence of c-kit mutation in all hematopoietic lineages and increased serum beta 2-microglobulin are the most powerful independent markers for predicting the transformation of indolent mastocytosis into a more aggressive form. In these patients, the prognosis depends largely on the course of the hematologic disease. Recent evidence indicates that patients with mastocytosis may be at increased risk of anaphylaxis to hymenoptera venom.[47] Therapy of mastocytosis is generally symptomatic in children. Psoralen plus

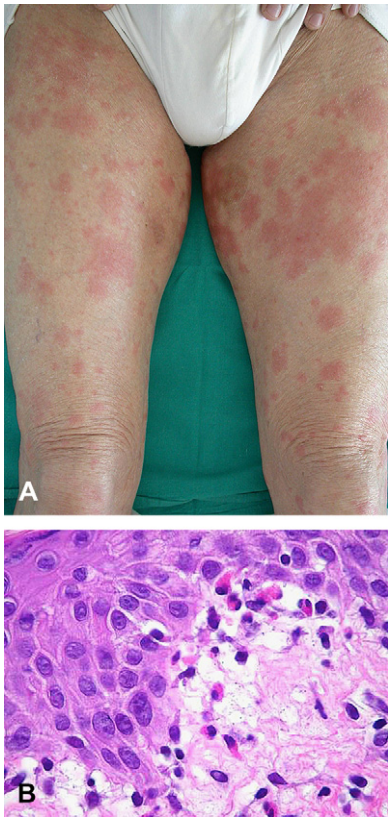

Fig 6. Bullous pemphigoid. **A**, Itchy urticarial lesions. **B**, Initial dermoepidermal detachment with an inflammatory infiltrate rich in eosinophils arranged to form microabscesses. (Hematoxylin–eosin stain; original magnification: ×400.)

ultraviolet A light phototherapy or UVA1 therapy is considered the first-line treatment for maculopapular skin lesions in adults.[48]

Autoimmune bullous diseases

Key points

- **Autoimmune bullous diseases are subepidermal blistering diseases, but may present solely with urticarial lesions in the early phases**
- **Skin lesions often have a symmetrical distribution, with predominant initial involvement of the trunk or flexor surfaces of the extremities**
- **Histology and antibody testing in serum and/or the skin are needed to confirm diagnosis**

Subepidermal autoimmune bullous diseases, including bullous pemphigoid, gestational pemphigoid, linear IgA dermatosis, and epidermolysis bullosa acquisita are diseases caused by the presence of autoantibodies directed against different basement membrane components, leading to the formation of a subepidermal blister.[49-54] These diseases are predominantly seen in adults or the elderly. Full-blown diseases are characterized by the presence of bullae of variable sizes arising on erythematous or normal skin. In some cases, bullous lesions are anticipated by itchy urticarial (Fig 6, *A*) or eczematous lesions or itch alone. In general, these lesions precede typical bullous lesions only by days or weeks; in cases where the urticarial phase lasts longer, the diagnosis of an autoimmune blistering disease may not be easily taken into account. In many cases, urticarial lesions coexist with bullous lesions. Lesions tend to have a symmetric distribution, with predominant initial involvement of the trunk or flexor aspects of the extremities. Intraepidermal blistering diseases (pemphigus) are not usually associated with urticarial prodromal or concurrent lesions, with the exception of pemphigus herpetiformis, which is a rare variant of pemphigus vulgaris with a more benign course.[55] A cutaneous biopsy is mandatory, and the diagnosis can be easily confirmed by histologic examination (Fig 6, *B*) plus direct immunofluorescence staining, which is still the criterion standard. Serum autoantibodies (anti-BP180, anti-BP230, and anti-desmogleins 1 and 3) are becoming a standard for the diagnosis and are now routinely evaluated in many centers. Occasionally, dermatitis herpetiformis of Duhring may also present with urticarial lesions along with the typical papulovesicles.[56]

Pruritic urticarial papules and plaques of pregnancy

Key points

- **PUPPP begins during the third trimester of pregnancy or soon after delivery**
- **PUPPP first appears as a small, fixed papular urticarial lesion, with progressive coalescence into plaques. Additional features may include eczematous changes, vesicles, or targetoid lesions**
- **PUPPP predominantly involves the trunk (abdomen) and proximal extremities**
- **Spontaneous complete resolution occurs within weeks**
- **A histologic examination reveals a nonspecific perivascular lymphohistiocytic infiltrate with some edema and eosinophils in the dermis; direct and indirect immunofluorescence studies are routinely negative**

PUPPP, also known as polymorphic eruption of pregnancy, is one of the most commonly diagnosed pruritic dermatoses of pregnancy, but it has a

confusing nomenclature because of the diversity of its cutaneous features.[57,58] The disease usually affects women during their first pregnancy, and the skin lesions classically appear in the third trimester (mean onset in the 35th week [range, 25-42]), and in extremely rare cases it first appears postpartum or earlier on in the pregnancy.[57,58] The etiology of PUPPP is still unknown; hormonal changes, connective tissue damage, and immunologic mechanisms are likely involved.[58] PUPPP typically presents with 1- to 2-mm erythematous papules that then coalesce to form urticarial plaques. With the disease progression, however, about half of the patients develop additional features, such as eczematous lesions with vesicles, polycyclic erythema, and/or targetoid or erythema multiforme–like lesions.[57] The lesions have a symmetrical distribution, and the primary location of the eruption is the abdomen (often within the striae distensae, but with periumbilical sparing), followed by the thighs, arms, and buttocks, with facial sparing.[57,58] No mucosal involvement is reported.[57] PUPPP is a benign disorder with a tendency toward spontaneous resolution after delivery; the mean disease duration (± standard deviation) is 4 ± 3 weeks (range, 1-16).[57] Recurrence in subsequent pregnancies, with menses or with the use of oral contraceptives is uncommon; recurrent PUPPP tends to be less severe than the first episode.[58] In contrast to gestational pemphigoid, it is not associated with fetal or maternal morbidity and mortality, but some studies have reported increased maternal weight gain and increased newborn birth weight.[57,59] There are no specific laboratory abnormalities; on histologic sections, a nonspecific perivascular lymphohistiocytic infiltrate with some edema and eosinophils in the dermis are observed. Direct and indirect immunofluorescence are routinely negative, a finding helpful in differentiating this entity from gestational pemphigoid.[57,58]

RARE CUTANEOUS URTICARIAL SYNDROMES

These include autoimmune progesterone/estrogen dermatitis, interstitial granulomatous dermatitis, eosinophilic cellulitis (Wells syndrome), neutrophilic eccrine hidradenitis (NEH), and urticaria-like follicular mucinosis.

Autoimmune progesterone dermatitis

Key points

- **Autoimmune progesterone/estrogen dermatitis is an uncommon recurrent disorder in females of reproductive age**
- **Skin lesions appear only or predominantly during the luteal phase of the menstrual cycle and they can be true wheals or eczematous, vesiculopustular, or erythema multiforme–like lesions**
- **Hallmarks for diagnosis include premenstrual flare, its prevention with the inhibition of ovulation, and positive skin reaction to intradermal injection of progesterone**
- **There are no specific histologic markers to support the diagnosis, and the features are variable according to the clinical type of lesion**

Autoimmune progesterone dermatitis is a rare disorder that is characterized by the monthly occurrence of polymorphous skin manifestations, flaring during the luteal phase of the menstrual cycle when progesterone levels peak. The eruption is considered to represent a hypersensitivity response to endogenous progesterone, and can occur in women with or without previous exogenous progesterone exposure. To date, no more than 60 cases have been reported. Cutaneous lesions appear or are markedly exacerbated during the luteal phase of the menstrual cycle, usually 3 to 10 days before the onset of menstrual flow; lesions resolve partially or completely a few days after menses.[60,61] Autoimmune progesterone dermatitis has also been reported in two postmenopausal women receiving oral progesterone replacement therapy for the treatment of climacteric symptoms.[62] Cutaneous manifestations are variable and include true urticaria (in approximately 50% of reported cases), urticarial eruptions, eczematous eruptions, vesiculopustular eruptions, fixed drug eruptions, stomatitis, erythema multiforme–like lesions, and anaphylaxis (about 10 cases).[63,64] There are no specific histologic markers to support the diagnosis, and the features may vary according to the clinical type of lesion.[65] The hallmarks for diagnosis include premenstrual flare, its prevention with the inhibition of ovulation, and positive skin reaction to intradermal injection of progesterone. Patch testing with various progesterone derivatives is negative.[63] The challenge test with intramuscular progesterone acetate is also rarely used for diagnosis.[63] This disease should not be confused with other dermatologic conditions that may be exacerbated perimenstrually, including lupus erythematosus, psoriasis, atopic eczema, lichen planus, dermatitis herpetiformis, erythema multiforme, and urticaria. In these other cases, lesions are usually present during the interim of time and are only aggravated during the luteal phase.[66] Fewer cases of estrogen autoimmune dermatitis, with severe premenstrual exacerbations, have been reported.[67,68]

Interstitial granulomatous dermatitis

Key points

- **Interstitial granulomatous dermatitis (IGD) is a rare adult onset disease, with diverse clinical presentations including papules, nodules, plaques, and urticarial rash**
- **IGD may be associated with articular involvement, and sometimes with autoimmune diseases**
- **A skin biopsy specimen shows interstitial and palisading granulomatous dermatitis associated with piecemeal fragmentation of collagen and elastic fibers**
- **IGD identifies a rather uniform histologic reaction pattern associated with variable clinical presentation. IGD is therefore a descriptive histologic term and does not identify a specific disease**

IGD is a rare clinical/pathologic entity first identified by Ackermann in 1993, and it is still in the process of definition. It may be best interpreted as a peculiar inflammatory reaction pattern with protean clinical presentation. In the international literature, about 60 cases have been reported to date, and the largest case series includes 17 patients.[69] It is primarily an adult onset disease with female predominance.[70] Cutaneous lesions can have very diverse characteristics: often they are papules, nodules, or plaques that are skin colored or erythematous to brown; however, the lesions are sometimes purely subcutaneous. Dimensions of the lesions can vary from a few to 20 cm and can have various shapes (oval, annular, or even cord-like), which is considered more indicative of the disease.[71] In some cases, the lesions are urticarial with persistent erythematous-edematous eruption. IGD is commonly associated with autoimmune diseases, including thyroiditis, diabetes, vitiligo, or connective tissue diseases. In the vast majority of patients, symmetrical seronegative and nonerosive polyarthritis is present, which can affect small or large joints.[70,71] Articular involvement may be progressive with joint destruction in more than half of the patients, whether or not it occurs along with rheumatoid arthritis.[72] A correlation with lymphoproliferative disorders, solid neoplasms (lung cancer), drugs, and infections has also been reported.[73] Therefore, although the nosographic categorization and the pathophysiologic interpretation remain elusive, the frequent association of IGD with autoimmune diseases or immunologic abnormalities renders an immune-mediated pathogenesis very likely. The granulomatous reaction may be induced by damage to collagen produced by the deposition of immune complexes in dermal vessel walls or by their diffusion into the dermal interstitium. On histologic examination, IGD shows an interstitial and palisading granulomatous dermatitis associated with piecemeal fragmentation of collagen and elastic fibers.[74] The inflammatory process extends from the mid-reticular dermis to the dermal–subcutaneous interface, whereas in other cases, a band-like distribution of interstitial granulomatous infiltrates is present.[74] Areas of histiocytic "rosette" formation around degenerating collagen in IGD are distinctive.[70] The presence of neutrophils in IGD defines the granuloma annulare–like lesions associated with systemic disorders.[75] The clinical and histopathologic diagnostic considerations of IGD with plaques include the inflammatory stage of morphea, the granulomatous variants of mycosis fungoides, Wells syndrome, leukemia cutis, granulomatous reactions to drugs, and in particular the erythematous or patch variant of granuloma annulare[70,72,74]; with the presence of cord-like lesions, Mondor disease, periarteritis nodosa, and larva migrans syndrome must be ruled out.[71] A histologic examination is mandatory for diagnosis, and clinical/pathologic correlation is essential in identifying the underlying associated conditions. In two-thirds of the cases, IGD shows a chronic course, with lesions lasting for months or years, but in other cases they can simply be recurrent and episodic, lasting only a few weeks.[70] The articular involvement usually evolves according to skin signs, but sometimes it is more persistent. Therefore, IGD is a descriptive histologic term rather than a specific disease, and its classification remains controversial. The recognition of IGD is important because it may indicate an underlying systemic autoimmune condition.

Eosinophilic cellulitis (Wells syndrome)

Key points

- **Wells syndrome appears clinically as localized or diffuse pruritic erythematous and edematous lesions, which evolve into plaques within a few days and resolve completely, leaving some hyperpigmentation. In some cases, bullous lesions are present**
- **Peripheral eosinophilia may be present in the acute phase, and a marked eosinophilic infiltrate is seen on histologic examination**
- **Lesions may recur**
- **The histologic features vary over time; eosinophilic infiltrate and flame figures are distinctive, although not pathognomonic**

Eosinophilic cellulitis (Wells syndrome) is a rare dermatosis that appears as acute pruritic erythematous and edematous lesions.[76,77] Cutaneous lesions

are variable in appearance and may be confused with cholinergic urticaria, cold-induced urticaria, urticarial vasculitis, cellulitis, persistent insect bite, contact dermatitis, or even with uniform giant red urticaria on angioedema.[77] Patients may present with one or a few erythematous lesions, which evolve into plaques over 2 to 3 days and disappear completely without scarring in 2 to 8 weeks. In some patients, lesions are widespread with a symmetrical or a more random distribution. The color of the plaques can vary from blue-gray to intensely erythematous and violaceous.[76] In some cases, bullous lesions develop, and the differential diagnosis may include subepidermal autoimmune bullous diseases.[78] The lesions tend to recur. Peripheral eosinophilia is present during the acute phase in approximately half of the cases,[79] and is useful but not essential in establishing the diagnosis. The histopathologic findings in this syndrome are characteristic and evolve over time. In the acute phase, dermal edema and a predominantly eosinophilic infiltrate are observed in the papillary and reticular dermis.[79] In the subacute phase, degranulating eosinophils coat basophilic collagen bundles with eosinophilic major basic protein; this latter finding is termed "flame figures" and is distinctive, but not pathognomonic, of Wells syndrome.[77,79] In the resolving stage, phagocytic histiocytes palisade around flame figures.[79] The diagnosis of Wells syndrome is based on both typical clinical features and histopathologic findings.[80] The etiology and pathogenesis are unknown. Wells syndrome may be idiopathic or associated with hematologic disorders, infections, arthropod bites, drug administration, or surgery.[77,80] It is important to differentiate Wells syndrome from the hypereosinophilic syndromes (see part II).

Neutrophilic eccrine hidradenitis

Key points

- **NEH is a very rare inflammatory dermatosis that presents as solitary or grouped fixed erythematous edematous papules and plaques. The disease is self-limiting, disappearing within days or weeks without scarring**
- **In the vast majority of cases, NEH affects patients with hematologic malignancies—in particular, acute myelogenous leukemia after receiving chemotherapy**
- **NEH is frequently associated with fever**
- **Histology shows a dense neutrophilic infiltrate surrounding and infiltrating the secretory portion of the eccrine glands, with focal epithelial cell necrosis and vacuolar degeneration of the eccrine coils**

NEH is a very rare, self-limiting inflammatory dermatosis seen primarily in patients with hematologic malignancies (90% of cases)—in particular, acute myelogenous leukemia after receiving chemotherapy.[81] Indeed, 84% of patients received chemotherapy before the onset of NEH, mainly cytarabine and anthracyclins; however, in other cases, patients received different drugs or none at all. NEH heralded malignancy or its relapse or, in other cases, it was associated with different clinical conditions (eg, Behçet's disease or infectious diseases).[81-83] A slight male predominance has been observed.[81] Clinical presentation can be variable, but NEH commonly presents as solitary or grouped erythematous edematous papules and plaques that are asymptomatic, pruritic, or painful.[81-83] In rare instances, lesions can be disseminated and show hyperpigmentation, purpura, or pustules.[81] The lesions are usually located on the proximal extremities, trunk, and periorbital region, but sometimes develop in a distal disposition, affecting only the extremities; the groin and axillae are usually spared.[81,82] Fever is frequent but it is most likely related to the underlying conditions.[81] In contrast to Sweet syndrome, no visceral neutrophilic infiltrate has been reported in NEH.[81] The histopathology of NEH is characterized by a dense neutrophilic infiltrate surrounding and infiltrating the secretory portion of the eccrine glands, with focal epithelial cell necrosis and vacuolar degeneration of the eccrine coils.[81-83] The neutrophilic infiltrate may also involve the eccrine ducts, usually sparing the acrosyringium.[81,83] Neutrophils can be found in the ductal lumina, possibly with abscess formation.[81] Diffuse dermal edema with perivascular infiltrate, consisting of lymphocytes, neutrophils, macrophages, and eosinophils, may also be seen.[82] The spontaneous resolution of lesions is always observed within a few days or weeks.[81,82] As a result, no specific treatment is required in most patients, but because of the associated systemic conditions, patients often receive antibiotics, NSAIDs, or oral corticosteroids—the latter seeming to shorten the duration of lesions and fever and to relieve pain.[81]

Urticaria-like follicular mucinosis

Key points

- **Urticaria-like follicular mucinosis is a very rare disorder that presents as fixed urticarial papules or plaques on the head or neck, within an erythematous seborrheic background**
- **Urticaria-like follicular mucinosis primarily affects middle-aged men**
- **There are no associated systemic diseases; it has a good prognosis**

- **Histologically, mucin-filled cystic spaces are seen in the outer sheath of the hair follicles, with slight inflammatory changes of the dermis**

Urticaria-like follicular mucinosis is a very rare disorder that was first described in 1980[84]; it is seen primarily in middle-aged men. It appears as urticarial papules or plaques on the head or neck within an erythematous seborrheic background. The intensity of the itch can vary and the lesions tend to resolve spontaneously, but they can recur irregularly over a period ranging from 2 months to 15 years.[84,85] As lesions resolve, red macules persist for a few weeks; hair-bearing regions can be involved, but neither follicular plugging nor alopecia are seen.[84] There are no associated systemic diseases, and prognosis is usually good.[85] On histologic examination, a typical pattern of follicular mucinosis can be seen: normal epidermis, slight edematous dermis with an inflammatory infiltrate in the papillary dermis, with lymphocytes and eosinophils around blood vessels and hair follicles, and mucin-filled cystic spaces in the outer sheath of the hair follicles.[85]

CONCLUSION

The diagnosis and treatment of urticaria is an everyday task for dermatologists. In the vast majority of cases, diagnosis is not difficult, although management may be challenging. When cutaneous lesions are not entirely typical, it is important to consider other cutaneous diseases that present with wheal-like lesions. Part 2 of this series will examine systemic diseases that present with urticarial lesions.

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Answers to CME examination

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1. c
2. b
3. d
4. b
5. a

Urticarial lesions: If not urticaria, what else? The differential diagnosis of urticaria

Part II. Systemic diseases

Anna Peroni, MD,[a,c] Chiara Colato, MD,[b] Giovanna Zanoni, MD,[c] and Giampiero Girolomoni, MD[a]
Verona, Italy

There are a number of systemic disorders that can manifest with urticarial skin lesions, including urticarial vasculitis, connective tissue diseases, hematologic diseases, and autoinflammatory syndromes. All of these conditions may enter into the differential diagnosis of ordinary urticaria. In contrast to urticaria, urticarial syndromes may manifest with skin lesions other than wheals, such as papules, necrosis, vesicles, and hemorrhages. Lesions may have a bilateral and symmetrical distribution; individual lesions have a long duration, and their resolution frequently leaves marks, such as hyperpigmentation or bruising. Moreover, systemic symptoms, such as fever, asthenia, and arthralgia, may be present. The most important differential diagnosis in this group is urticarial vasculitis, which is a small-vessel vasculitis with predominant cutaneous involvement. Systemic involvement in urticarial vasculitis affects multiple organs (mainly joints, the lungs, and the kidneys) and is more frequent and more severe in patients with hypocomplementemia. Clinicopathologic correlation is essential to establishing a correct diagnosis. (J Am Acad Dermatol 2010;62:557-70.)

Learning objectives: After completing the learning activity, participants should be able to distinguish urticarial lesions suggesting diagnoses other than common urticaria; assess patients with urticarial lesions, and suspect systemic diseases presenting with urticarial skin lesions.

Key words: autoinflammatory syndromes; hypereosinophilic syndromes; neutrophilic urticarial dermatosis; Schnitzler syndrome; urticaria; urticarial vasculitis.

Urticaria is a common disorder that is classically distinguished into acute and chronic forms, which are similar clinically but differ substantially in etiology, epidemiology, patient approach, therapy, and prognosis.[1-3] Ordinary urticaria does not have systemic implications, with the exception of the association with autoimmune thyroid diseases,[4] and does not present with systemic symptoms. The diagnosis of urticaria may not always be straightforward. The differential diagnosis between common urticaria and urticarial diseases limited to the skin was discussed in part I of this two-part series. The presence of systemic symptoms—in particular, fever, asthenia, and arthralgia—and neurologic, respiratory, or cardiovascular signs should alert physicians about the possibility that an urticarial rash is not ordinary urticaria but rather a systemic syndrome with urticaria-like skin lesions. Systemic urticarial

Abbreviations used:

CINCA:	chronic infantile neurologic cutaneous and articular syndrome
CMRO:	chronic recurrent multifocal osteomyelitis
COPD:	chronic obstructive pulmonary disease
DIF:	direct immunofluorescence
FCAS:	familial cold autoinflammatory syndrome
FMF:	familial Mediterranean fever
HIDS:	hyperimmunoglobulinemia D with periodic fever syndrome
MWS:	Muckle–Wells syndrome
PAPA:	pyogenic arthritis–pyoderma gangrenosum–acne syndrome
SLE:	systemic lupus erythematosus
TRAPS:	tumor necrosis factor receptor–associated periodic fever
UV:	urticarial vasculitis
HUV:	hypocomplementemic UV
NUV:	normocomplementemic UV

From the Department of Biomedical and Surgical Sciences,[a] Section of Dermatology and Venereology, and the Departments of Pathology, Sections of Pathology[b] and Immunology,[c] University of Verona, Italy.

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Correspondence to: Giampiero Girolomoni, MD, Clinica Dermatologica, Università di Verona, Piazzale A. Stefani 1, 37126 Verona, Italy. E-mail: giampiero.girolomoni@univr.it.

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syndromes are very heterogeneous and may involve many organs and systems (Table I). The objective of this article is to discuss the major clinical features of such systemic conditions resembling urticaria.

SYSTEMIC URTICARIAL SYNDROMES

The most important and common differential diagnosis with common urticaria is urticaria vasculitis (UV), which can be the cutaneous expression of a systemic disorder. Other systemic diseases that manifest with urticarial skin lesions are more rare but nonetheless very important to suspect. Systemic urticarial syndromes include other vasculitides (Churg–Strauss syndrome and polyarteritis nodosa), neutrophilic urticarial dermatosis, hematologic diseases (Schnitzler syndrome, Waldenström macroglobulinemia, and hypereosinophilic syndromes), and autoinflammatory diseases (Table II).

CAPSULE SUMMARY

- The presence of systemic symptoms should signal the possibility that an urticarial rash is not ordinary urticaria but rather a systemic syndrome with urticaria-like skin lesions.
- A thorough clinical evaluation is fundamental; particular attention should be paid to osteoarticular, neurologic, respiratory, or cardiovascular signs and symptoms.
- Systemic urticarial syndromes may manifest with skin lesions other than wheals. Lesions are more likely to have a bilateral and symmetrical distribution, individual lesions have a long duration, and their resolution frequently leaves marks, such as hyperpigmentation or bruising.
- Clinicopathologic correlation is essential to making the diagnosis.

Urticarial vasculitis and other vasculitides

Key points

- **UV is a small-vessel vasculitis with predominant skin involvement that represents the main differential diagnosis with chronic urticaria**
- **It manifests with urticarial skin lesions persisting for more than 24 hours, burning rather than itching, and resolving with hyperpigmentation or bruising. Other skin lesions (purpura or necrosis) may be associated**
- **UV is often associated with systemic diseases, particularly connective tissue diseases, and therefore systemic symptoms can be present**
- **Rarely, Churg–Strauss syndrome and polyarteritis nodosa may be associated with cutaneous urticarial lesions**
- **A biopsy for histologic examination is necessary in order to establish the diagnosis**

Vasculitis is a pathologic process characterized by inflammation and necrosis of the blood vessels that may or may not be accompanied by fibrin deposits and leukocytoclasia; red blood cell extravasation and perivascular inflammatory cell infiltrates are also present. Cutaneous small-vessel vasculitis is the most common type of vasculitis, and primarily affects cutaneous postcapillary venules. UV is a small-vessel vasculitis with predominant skin involvement manifesting with urticarial lesions. The clinical course of UV is characterized by exacerbations and remissions.[5] The duration of UV tends to be limited to several months, although there is a reported duration of 23 years.[6] Moreover, recurrences are reported.[6] UV is clinically characterized by wheals lasting for more than 24 hours and accompanied by burning or painful sensations and pruritus (Fig 1, *A*).[5,7,8] Wheals frequently resolve with residual hyperpigmentation or bruising. More rarely, other skin lesions (eg, purpura, necrosis, and ulcers) can be seen either simultaneously or in different phases (Fig 1, *B* and Fig 2, *A*).[7,9,10] In some cases, with the diascopy technique, previously unapparent purpura can be revealed as a dark red or brown macule in the center of an erythematous lesion.[11] Moreover, a large number (up to 40-60%) of patients may present only with wheals.[7,12] Therefore, a skin biopsy should be obtained in all cases of otherwise clinically typical chronic urticaria, especially if the urticaria is resistant to antihistaminic treatment, in order to exclude UV.[5,12] Angioedema is present in less than half of the patients.[5,7,8,12] Other cutaneous findings may include digital infarction, Raynaud phenomenon, photosensitivity, erythema gyratum repens–like eruption, and hemorrhagic vesicles.[6-8,13-15] The diagnosis always requires histologic confirmation. As for other vasculitides, the choice of the lesion to biopsy is essential. Full blown lesions reveal a vasculitis of the small dermal vessels, usually leukocytoclastic, which is characterized by a neutrophilic perivascular infiltrate, endothelial cell injury and swelling, neutrophil fragmentation, nuclear dust, erythrocyte extravasation, and fibrin deposition in and around the vessels (Fig 2, *B* and *C*).[6,8,10] More rarely, histology reveals a predominance of mononuclear (lymphocytes) cells with only a few granulocytes.[9,10] A major concern is that it is not always easy to detect true vasculitic changes.[11] Furthermore, a continuum of histologic changes exists between common urticaria and UV.[16] In addition, some patients may

Table I. Distinguishing features between urticaria and systemic urticarial syndromes

Common urticaria	Urticarial lesions (one or more of the following)
Only typical wheals:	Atypical "wheals":
Erythematous edematous lesions	Infiltrated plaques
Transient (<24-36 hrs)	Persistent (>24-36 hrs)
Asymmetric distribution	Symmetric distribution
Resolution without signs	Resolution with signs (hypo/hyperpigmentation, bruising, or scarring)
No associated different elementary lesions (papules, vesicles, purpura, or crustae, etc)	Associated different elementary lesions (papules, vesicles, purpura, scaling, or crustae, etc)
Pruritic (rarely stinging/burning)	Not pruritic; rather painful or burning
Possibly associated with angioedema	Usually no associated angioedema
No associated systemic symptoms	Often associated with systemic symptoms (ie, fever, malaise, arthralgia, abdominal pain, weight loss, acral circulatory abnormalities, or neurologic signs

Table II. Principal systemic diseases or syndromes that can manifest with urticarial lesions

Vasculitides and immunologic disorders
- Urticarial vasculitis
- Systemic lupus erythematosus
- Sjögren syndrome
- Dermatomyositis
- Mixed connective tissue disease
- Juvenile rheumatoid arthritis
- Churg–Strauss disease
- Wegener granulomatosis
- Polyarteritis nodosa
- Neutrophilic urticarial dermatosis

Hematologic diseases
- Non-Hodgkin lymphoma (B-cell)
- Waldenström macroglobulinaemia
- Schnitzler syndrome
- Monoclonal gammopathies of uncertain significance
- Cryoglobulinemia
- Hypereosinophilic syndromes
- Episodic angioedema with eosinophilia (Gleich syndrome)
- Polycythemia vera

Autoinflammatory syndromes

Hereditary periodic fever syndromes
- Familial Mediterranean fever
- Tumor necrosis factor receptor–associated periodic fever
- Hyperimmunoglobulinemia D with periodic fever syndrome

Cryopyrin-associated periodic syndromes
- Familial cold autoinflammatory syndrome
- Muckle–Wells syndrome
- Neonatal onset multisystem inflammatory disease (chronic infantile neurologic cutaneous and articular syndrome)

Others
- Pyogenic arthritis-pyoderma gangrenosum-acne syndrome
- Blau syndrome
- Chronic recurrent multifocal osteomyelitis and Majeed syndrome

concomitantly have UV and common urticaria. The incidence of UV is about 5% to 10% of those with chronic urticaria (up to 15% in antihistamine-resistant cases), and the majority of these are women (57-70%), with a peak age in the fourth decade of life.[7,8,11,12] Fewer than 10 pediatric cases of UV have been reported in the last 20 years, with a female predominance (about two thirds) and an age varying from 9 months to 12 years; the principal associated manifestations were renal involvement (3 cases), pulmonary disease (2 cases), and systemic lupus erythematosus (SLE; 2 cases), with hypocomplementemia in the majority of cases (5 of 7 cases).[17-23] Although UV is a sporadic disease, a pair of identical twins with hypocomplementemic UV (HUV) has been reported.[24]

UV is believed to result from the deposition of immune complexes on the blood vessel wall. Immune complexes have been found in the circulation of 30% to 75% of patients with UV.[25] The antigens eliciting the formation of antibodies are often not known. UV is more often idiopathic, but in some cases eliciting stimuli have been identified. One such stimulus may be drugs, including antifolate agents (methotrexate and pemethrexate),[26,27] antidepressants (paroxetine and fluoxetine),[28,29] appetite suppressants,[30] infliximab,[31] procainamide,[32]

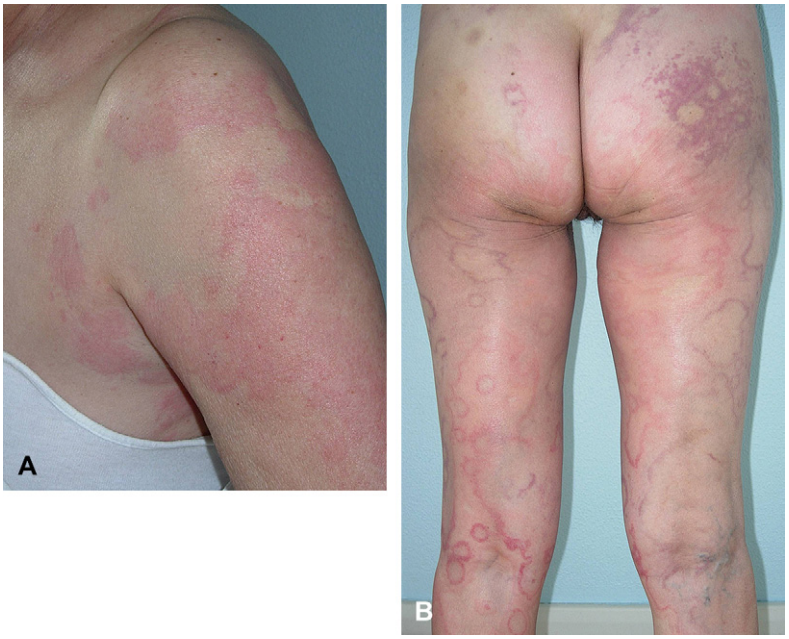

Fig 1. Urticarial vasculitis. **A**, Typical wheals on the trunk and upper limbs coexist in the same patient with (**B**) figurate hemorrhagic, livedoid lesions in the lower limbs subsequent to urticarial lesions.

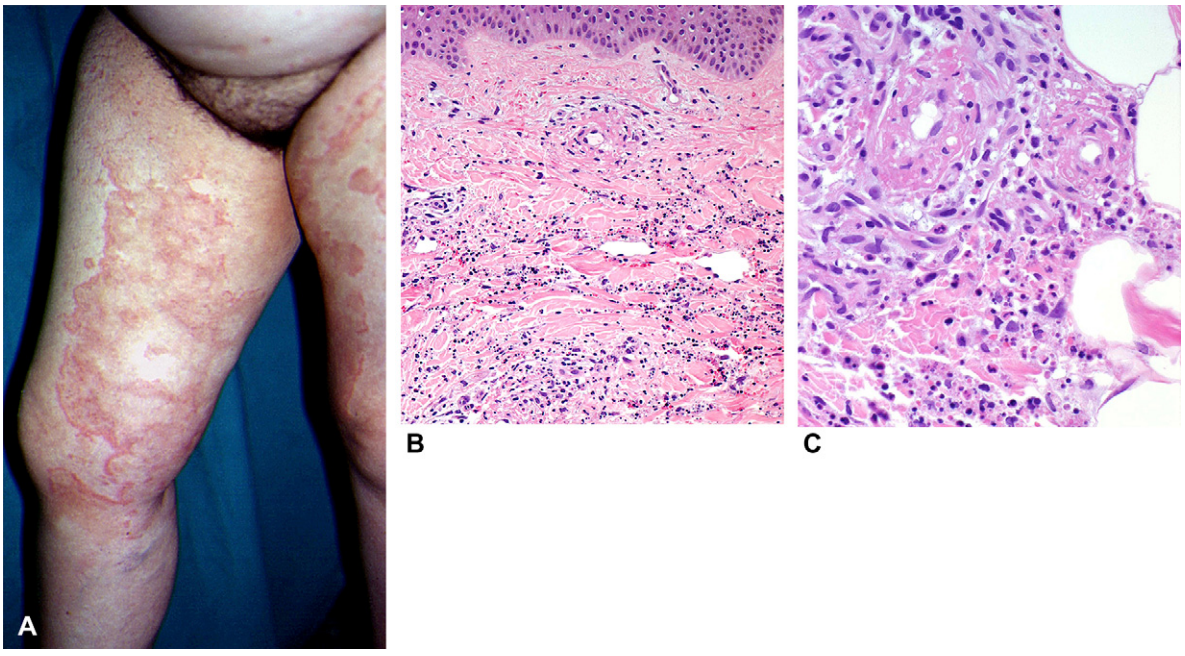

Fig 2. Urticarial vasculitis. **A**, Urticarial purpuric lesions in the lower limbs leaving residual hyperpigmentation. **B** and **C,** Leukocytoclastic vasculitis with fibrinoid necrosis of the vessel wall and abundant infiltrate of neutrophils and nuclear dust. (Hematoxylin–eosin stain; original magnifications: **B**, ×100; **C**, ×250.)

cimetidine,[33] sulfamethoxazole-trimethoprime,[34] and other substances (herbs, cocaine, bacillus Calmette-Guérin vaccine, and formaldehyde).[35-38] Moreover, rare cases induced or exacerbated by physical stimuli have been reported, including sun or ultraviolet light exposure,[39,40] cold,[41,42] and physical exercise.[43] In some UV patients, a collagen-like region of the complement fragment C1q has been

implicated as the target antigen.[10,44] Indeed, a portion of the patients with HUV also have anti-C1q antibodies. These anti-C1q antibodies have been described to be very common in HUV and in SLE, hepatitis C, rheumatoid arthritis, and particularly in patients with glomerulonephritis.[45] Anti-C1q antibodies are reported to be predictive of active renal involvement.[44] Furthermore, patients with UV and anti-C1q antibodies frequently have chronic obstructive pulmonary disease[11] and other symptoms, such as arthritis or arthralgia, uveitis/episcleritis, recurrent abdominal pain, and glomerulonephritis, as first described by McDuffie et al[46] and Schwartz et al[47] and proposed by Wisnieski[10] to be a separate entity (hypcomplementemic urticarial vasculitis syndrome).

UV can be a local process unassociated with an underlying disease or it can be the presenting manifestation of a systemic disease. Among these, the most common are autoimmune connective tissue diseases (particularly SLE,[19,20,48-55] but also systemic sclerosis,[56] Gougerot–Sjögren syndrome,[57] and paraneoplastic dermatomyositis[58]), followed by infections (mainly chronic or acute viral hepatitis[59-64] and sporadic reports of Epstein–Barr virus,[65] *Mycoplasma pneumoniae*,[66] and Lyme disease[67]) and inflammatory bowel diseases.[68] In some cases, UV can be a paraneoplastic manifestation, mainly associated with hematologic malignancies, including mostly non-Hodgkin B-cell lymphomas,[69-71] monoclonal gammopathies/myeloma,[72-74] anecdotal cases of Castleman disease,[75] and polycythemia rubra vera,[76] but also with various solid neoplasms (non–small cell lung cancer,[77] renal cancer,[78] testicular teratoma,[79] colon adenocarcinoma,[80] and nasopharyngeal carcinoma[58]). Finally, the vasculitic process that causes skin lesions can also involve internal organs, particularly the joints, kidneys, and lungs, and also the gastrointestinal tract and central and peripheral nervous systems.

It is noteworthy to mention that UV can be further divided into two groups according to classical pathway complement levels (mainly total complement, CH50, or C3 and C4 fragments): normocomplementemic UV (NUV) and HUV. These two subtypes of UV have significantly different clinical characteristics, as shown in Table III, which summarizes data from the four major case series published in the English literature in the last 20 years.[5,7,8,12] HUV is strongly associated with female gender (60-100%), the presence of purpura and/or residual hyperpigmentation after skin lesions have faded, and the diagnosis of SLE.[5,7,8] Moreover, 40% to 80% had arthralgias and 71% to 78% had antinuclear antibodies, suggesting that HUV is a subset of SLE.[5,8,12] Patients with HUV also more frequently show renal and pulmonary involvement.[5,7,8,12] In contrast, patients with normal complement levels on repeated determinations tend to have less frequent systemic involvement. They also show a higher prevalence of females (52-60%), although to a lesser extent. NUV patients possibly have systemic manifestations or the presence of antinuclear antibodies, but only a minority of them meet the criteria for SLE.[5,8,9] Patients with NUV have a more benign prognosis than HUV patients, but in both cases death as a result of the primary disease is rare, mostly secondary to pulmonary involvement.[9,81] Articular involvement, either arthralgia or arthritis, is the most frequent finding in both groups, although significantly more prevalent in HUV compared to NUV. Articular manifestations tend to be migratory and transient, mostly affecting peripheral joints.[9] Jaccoud arthropathy (chronic deforming synovitis, without loss of cartilage or bone erosion of the joints of hands and feet and deviation of the fingers) is rarely reported in patients with HUV, and tends to be associated with valvular heart disease.[82-87] Cardiac involvement is reported also without Jaccoud arthropathy, in the form of valvular heart disease,[88,89] recurrent pericarditis with tamponade,[90,91] and myositis involving the heart and proximal muscles[92] exclusively in HUV patients. Lung involvement occurs frequently in HUV and is more severe in smokers.[47] The predominant pulmonary manifestation is chronic obstructive pulmonary disease (COPD).[5,7,47] It is characterized histopathologically by capillaritis[93] or leukocytoclastic vasculitis of pulmonary venules,[94] causing an increase in the number of neutrophils that release elastases, leading to tissue destruction that eventually results in emphysema.[9,95] Other rare findings include pleural effusion[96] and a restrictive functional pattern[63]; in pediatric patients, pulmonary hemosiderosis and hemorrhages have been reported.[18,23] Disease response to therapy and severity are variable, leading in very rare cases to lung transplantation or death.[93,97] Renal disease is frequent, and may include a variety of processes, such as glomerulonephritis (the most frequent form), interstitial nephritis, and necrotizing vasculitis.[5,7,8,9,11] According to isolated case reports, it affects HUV patients almost exclusively, with only rare cases reported in NUV patients in the larger case series.[8,7,12] Two cases of renal involvement are reported also in pediatric HUV patients.[22,23] In very rare cases, renal disease led to nephrotic syndrome, kidney transplant, or death.[97-100]

Gastrointestinal symptoms occur often and more frequently in HUV; they include nausea, vomiting, abdominal pain, and diarrhea, but usually not gastrointestinal bleeding or ischemia.[9,101] Occurring

Table III. Differences between hypocomplementemic and normocomplementemic urticarial vasculitis*

	Hypocomplementemic UV						Normocomplementemic UV						
	Merhegan et al[7]	Davis et al[5]	Dincy et al[8]	Tosoni et al[12]	Total	%	Merhegan et al[7]	Davis et al[5]	Dincy et al[8]	Tosoni et al[12]	Total	%	$P^{\dagger}$
Total no. of patients in cohort	72	132	68	47			72	132	68	47			
No. of patients with the specific UV type	23	24	14	5	66		49	108	54	42	253		
Females	NS	24	11	NS	35/38	92	NS	65	28	NS	93/162	57	.000
Fever	1	3	6	3	13/66	20	3	12	9	14	38/253	15	.462
Arthralgias/arthritis	18	18	6	4	46/66	70	21	26	16	14	77/253	30	.000
Abdominal pain	8	NS	0	1	9/42	21	7	NS	6	1	14/145	10	.075
Renal involvement	2	3	3	1	9/66	14	2	0	1	10	13/253	5	.031
Lung involvement	6	4	1	0	11/66	17	3	5	0	6	14/253	6	.006
Purpura/residual hyperpigmentation	15	NS	NS	3	18/28	64	10	NS	NS	0	10/91	11	.000
Systemic lupus erythematosus	5	13	NS	NS	18/47	38	3	2	NS	NS	5/157	3	.000
Increased sedimentation rate	NS	12	NS	2	14/29	48	NS	26/89	NS	18	44/131	34	.202
Antinuclear antibodies presence	NS	17	11	NS	28/38	74	NS	26/97	7/46	NS	33/143	23	.000
Fluorescent deposits at DEJ[‡]	16	NS	1/10	NS	17/33	52	9	NS	0/3	NS	9/51	18	.002
Fluorescent deposits around dermal vessels[‡]	20	NS	2/10	NS	22/33	67	14	NS	2/3	NS	16/51	31	.003
Fluorescent deposits at DEJ + dermal vessels[‡]	NS	23	5/10	NS	28/33	85	NS	1	1/3	NS	2/111	2	.000
Neutrophilic predominance (interstitial)	16	19	12	NS	47/61	77	21	11	34	NS	66/211	31	.000
Eosinophil presence	NS	1	11	NS	12/38	32	NS	7	47	NS	54/162	33	.988

DEJ, Dermoepidermal junction; *NS*, absolute number not specified or data not recorded; *UV*, urticarial vasculitis.
*Data derived from the four studies indicated have been aggregated and compared by using the χ^2 test.
†Differences between hypocomplementemic and normocomplementemic urticarial vasculitis.
‡Fluorescent deposits mainly of immunoglobulin G and C3.

more often in HUV, neurologic complications are not frequent but are possible in both HUV and NUV. They include pseudotumor cerebri, seizure, transverse myelitis, and lower cranial nerve palsies or peripheral neuropathy.[8,102-105] Ocular involvement is severe, but infrequent, with conjunctivitis, recurrent uveitis, scleritis, or optic disc and retinal vasculitis occurring almost exclusively in patients with HUV.[5,9,106-108] Therefore, UV associated with systemic involvement is more likely to be hypocomplementemic, but lower than normal levels of complement may not result following a single determination, and may require multiple testings. Patients with UV and mild or no systemic symptoms but hypocomplementemia need a careful follow-up. Interestingly, a correlation has emerged between the dermal interstitial neutrophilic predominance and the presence of hypocomplementemia.[5,7,8,109] Direct immunofluorescence (DIF) may show deposits of immunoglobulins, complement or fibrin around blood vessels in about 70% to 80% of patients with active lesions in both HUV and NUV.[6,11] DIF positivity for IgG and/or C3 (especially at the basement membrane) is much more frequent in HUV.[5,7,8]

Treatment of UV is aimed first at controlling any underlying condition and second at controlling symptoms. No controlled trials are available on UV therapy. Antihistamines are useful for the symptomatic control of pruritus, but are rarely used alone. Corticosteroids of varying dosages are the mainstay of treatment, particularly in patients with HUV or a systemic disease; typically, systemic corticosteroids are initially administered at the dosage of 1 mg prednisone equivalent/kg daily until clinical remission is achieved, then slowly tapered off.[25] Because many patients have relapses after steroid tapering, it is often necessary to proceed to a maintenance treatment and add a steroid-sparing agent.[25] In these cases, dapsone may be the drug of choice, either alone[51,110-112] or in association with other agents[51,113,114]; in particular, it is effective in patients with a SLE-like presentation of UV.[25] Colchicine[112,115-118] and hydroxychloroquine[119] have also been used with some success. Mycophenolate mofetil has also been effective in the treatment of UV and as maintenance therapy.[106,120] Methotrexate is not considered to be particularly effective, although some patients may respond well.[121] Treatment with interferon-alfa could be considered in patients with UV and a hepatitis virus C infection.[61,62] Other treatments reported include cyclosporine A,[98] azathioprine,[122] cyclophosphamide with pulse dexamethasone,[106,123] rituximab,[49] intravenous immunoglobulins,[124] anakinra,[125] and plasmapheresis.[9,25]

Churg–Strauss syndrome, also known as allergic granulomatous angiitis, mostly affects middle-aged men and is characterized by a long multistep progression; in the initial years, patients have respiratory manifestations, such as rhinitis, nasal polyps, and asthma; then blood and tissue eosinophilia with Löffler infiltrates appears, followed by pneumonia and gastroenteritis, and finally multiorgan vasculitis may emerge.[126] Cutaneous manifestations are present in about half of the patients, including palpable purpura, petechiae, nodules, maculopapules, and livedo reticularis; urticarial lesions are present in less than 10% of patients.[127-129] Upon histologic examination, urticarial lesions may only reveal abundant eosinophil perivascular infiltration, whereas different cutaneous lesions show extravascular granulomas, small-vessel leukocytoclastic vasculitis with predominantly eosinophilic infiltrate, or cutaneous polyarteritis nodosa.[127] Approximately 6% of cases of polyarteritis nodosa have urticarial manifestations.[130]

Neutrophilic urticarial dermatosis

Key points

- **Neutrophilic urticarial dermatosis is a rare condition characterized by a transient urticarial eruption with a rich neutrophilic dermal infiltrate, both perivascular and interstitial**
- **It is a reaction pattern associated with connective tissue diseases and autoinflammatory syndromes**

Neutrophilic urticarial dermatosis is characterized clinically by an urticarial rash and histopathologically by a neutrophilic dermatosis. About 50 cases have been reported.[131] Skin lesions appear as erythematous macules, papules, or plaques that may resolve within 24 hours. Histologic examinations reveal an intense perivascular and interstitial neutrophilic infiltrate with leukocytoclasia but without vasculitis or dermal edema. Neutrophils also have a peculiar linear deposition between the dermal collagen fibers; necrobiotic isolated collagen fibers can be found in some cases. These features differentiate neutrophilic urticarial dermatosis with neutrophil dominated common urticaria. The absence of edema is useful in differentiating neutrophilic urticarial dermatosis from Sweet syndrome, whereas the absence of vasculitis can help in excluding UV. Finally, early stages of interstitial granulomatous dermatitis can be difficult to distinguish from neutrophilic urticarial dermatosis.[131] In the majority of patients, skin lesions are associated with systemic symptoms, such as fever and polyarthritis, or laboratory abnormalities, such as increased erythrocyte

sedimentation rate and leukocytosis.[131] Indeed, neutrophilic urticarial dermatosis is often associated with a systemic disease, most often adult-onset Still disease, lupus erythematosus, Schnitzler syndrome, paraproteinemia, or an autoinflammatory genetic disease.[131] The rash is chronic or recurrent and difficult to treat. It is usually unresponsive to antihistamines. The nosographic position of neutrophilic urticarial dermatosis is still debated, and it may eventually be found that this condition is not a separate condition but rather a reaction pattern common to different diseases.

Hematologic diseases

Key points

- **Urticarial lesions may be the manifestation of a variety of hematologic disorders**
- **Schnitzler syndrome presents as chronic urticarial lesions, immunoglobulin M (IgM) gammopathy, fever, and arthralgia**
- **Waldenström macroglobulinemia and cryoglobulinemia may be also associated with urticarial lesions and urticarial vasculitis**
- **Hypereosinophilic syndromes, particularly the lymphocytic variant, often show skin manifestations along with internal organ damage. Cutaneous findings include either angioedematous and urticarial lesions, or erythematous, pruritic papules and nodules**
- **Gleich syndrome is also characterized by recurrent episodes of angioedema and urticaria, eosinophilia, elevated serum IgM, fever, and increased body weight; however, it is not associated with internal organ damage**

Schnitzler syndrome is a rare and often misdiagnosed disease that is characterized by the simultaneous occurrence of monoclonal IgM gammopathy and chronic urticaria with at least two additional minor symptoms: arthralgia, bone pain, fever of uncertain origin, hepato- or splenomegaly, lymphadenopathy, increased erythrocyte sedimentation rate, leukocytosis/thrombocytosis, and increased bone density.[132,133] Monoclonal gammopathy can be detectable even some years after the onset of the cutaneous manifestations. No spontaneous remissions have been reported to date.[133] Schnitzler syndrome usually has a benign course and patients show no increased mortality during the follow-up periods, but there is a 10-year 15% risk of developing a lymphoproliferative disorder, most notably Waldenström macroglobulinemia.[133,134] Skin manifestations of Schnitzler syndrome include persistent urticarial lesions, frequently with figurate lesions, leaving a brown hyperpigmentation. Histologic examination reveals a perivascular mixed inflammatory infiltrate with leukocytoclasis, nuclear dust without fibrinoid necrosis, and extravasated red blood cells. IgM deposits can be seen at the dermoepidermal junction. Current treatment is often unsatisfactory, and includes high systemic doses of corticosteroids and antihistamines.[135] Recent evidence has demonstrated positive responses to oral cyclosporine, intravenous pulse cyclophosphamide, pefloxacin mesylate, and anakinra, the latter suggesting a possible autoinflammatory pathogenetic mechanism for this syndrome.[132,133,135]

Waldenström macroglobulinemia is a low-grade chronic B-cell lymphoproliferative disorder characterized by bone marrow infiltration with small lymphocytes, lymphoplasmacytoid cells, and plasma cells associated with an elevated circulating level of IgM paraprotein. It can be associated with cutaneous manifestations, such as purpura, edema, urticaria, and ulceration, which are the consequence of hyperviscosity, cryoglobulinemia, and/or tissue depositions of immunoglobulins; direct cutaneous infiltration by neoplastic lymphoid cells is less common and usually skin changes occur in later stages of the disease.[136]

Hypereosinophilic syndromes constitute a heterogeneous group of disorders, defined as persistent and marked blood eosinophilia ($>1.5 \times 10^9$/L for more than 6 consecutive months) associated with evidence of eosinophil-induced organ damage, where other causes of hypereosinophilia—such as allergic and parasitic disorders, solid and hematologic malignancies, Churg–Strauss disease, and HTLV infection—have been excluded.[137-139] Once these criteria are fulfilled, further testing for eventual pathogenic classification is warranted using the appropriate cytogenetic and functional approach.[137,138] The classification of these disorders is complex and still in progress, though it is possible to grossly divide them into intrinsic eosinophil disorders (myeloproliferative form), secondary to the clonal expansion of cells of the myeloid lineage with preferential eosinophilic differentiation, and extrinsic eosinophils disorders (lymphocytic form), secondary to an increased eosinophilopoietic cytokines production by other cell types, mainly TH_2 lymphocytes.[137,138] Hypereosinophilic syndromes occur most frequently in young to middle-aged patients, but they may affect any age group. There is a clear but still unexplained male predominance (male to female ratio, 4-9:1) in the myeloproliferative form, but not in the lymphoproliferative one.[137,140] Target-organ damage mediated by eosinophils is highly variable among patients, with involvement of the skin, heart, lungs, and central and peripheral

nervous systems in more than 50% of cases. Other frequently observed complications include hepato- and/or splenomegaly, eosinophilic gastroenteritis, and coagulation disorders.[137] Cutaneous manifestations are common and nonspecific and generally consist of angioedematous and urticarial lesions, very itchy erythematous papules and nodules, or eczematous lesions. In patients with the extrinsic lymphocytic variant, skin lesions are often the predominant clinical presentation. Mucosal ulcerations are possible, particularly in patients with the clonal myeloproliferative variant associated with the FIP1L1-PDGFRA fusion gene, and are an index of a poorer prognosis.[137,139] Therapeutic management should be adjusted according to the disease severity and variants and include corticosteroids, hydroxyurea (also named hydroxycarbamide), interferon-alfa, and imatinib mesilate.[137] Episodic angioedema with eosinophilia, or Gleich syndrome, also belongs to eosinophilic diseases, because it is characterized by recurrent episodes of angioedema and urticaria, eosinophilia, elevated serum IgM levels, fever, increased body weight, and a benign course.[141] Gleich syndrome does not show involvement of internal organs and could therefore be considered a clinical entity distinct from the hypereosinophilic syndromes,[140] although recent evidence of clonal T-helper lymphocytes and elevated interleukin-5 levels suggests its inclusion in the spectrum of the lymphocytic form of hypereosinophilic syndromes.[142]

Autoinflammatory syndromes

Key points

- **Autoinflammatory syndromes are a group of heterogeneous monogenic diseases that are characterized by recurrent episodes of multisystemic and seemingly unprovoked inflammation, most commonly caused by an excessive activation of the IL-1β pathway**
- **Skin lesions, fever, and arthralgia/arthritis are the most common symptoms. Cutaneous lesions frequently have an urticarial appearance, especially in the cryopyrinopathies and in familial Mediterranean fever, whereas erythematous macules and papules predominate in the other diseases of this group. Skin lesions are temporally associated with relevant systemic symptoms**
- **Histologically, cutaneous lesions generally show a perivascular neutrophilic infiltrate, sometimes with lymphocytes**

Autoinflammatory syndromes are a group of heterogeneous monogenic diseases that are clinically characterized by recurrent episodes of multisystemic, seemingly unprovoked inflammation. Indeed, these diseases are caused by variations, mostly missense mutations, in very few genes encoding for innate immune system components (mainly parts of the inflammasome), with the activation of the IL-1β pathway as the final unifying pathogenetic mechanism.[143] This latter fact explains the positive results obtained with anakinra, a recombinant human interleukin 1 receptor antagonist, in treating these patients; furthermore, a more specific anti–IL-1β antibody (canakimumab) proved to be effective in these patients and is awaiting approval from regulatory agencies.[143] This category traditionally includes the hereditary periodic fever syndromes, namely familial Mediterranean fever (FMF), tumor necrosis factor receptor–associated periodic fever (TRAPS), hyperimmunoglobulinemia D with periodic fever syndrome, and the cryopyrinopathies: familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and neonatal onset multisystemic inflammatory disease (NOMID, also called chronic infantile neurologic cutaneous and articular syndrome, or CINCA syndrome).[144] The detailed description of these diseases is beyond the purpose of this work, and they have recently been reviewed.[144] Moreover, other classifications have been proposed that include other diseases such as Blau syndrome, pyogenic arthritis-pyoderma gangrenosum-acne (PAPA) syndrome, chronic recurrent multifocal osteomyelitis (CRMO; Fig 3, *A*), hereditary angioedema, Behçet disease, Gaucher disease, and gout.[145,146] Particularly for this latter disease, there is evidence that monosodium urate crystals are specifically detected via the NALP3 inflammasome, resulting in a stimulation of IL-1β secretion.[147,148]

Autoinflammatory diseases present clinically with recurrent episodes of inflammation (fever, rashes, and elevation of acute phase reactants) in the absence of an infectious, neoplastic, or autoimmune etiology. Fever is always present, with variable duration and severity, along with different types of joint and skin involvement. Other variably associated systemic symptoms include abdominal pain, ocular findings, amyloidosis, serositis, myalgias, and neurologic signs.[144] These diseases are usually familial, but there is a growing number of identified sporadic cases.[149] Most cases present in childhood or infancy; few cases are first detected in adulthood. Cutaneous lesions have an urticarial appearance ("urticarial rash"), especially in the cryopyrinopathies and in FMF, whereas in the other diseases previously mentioned erythematous macules and papules predominate; other skin lesions, such as purpura, vasculitis,

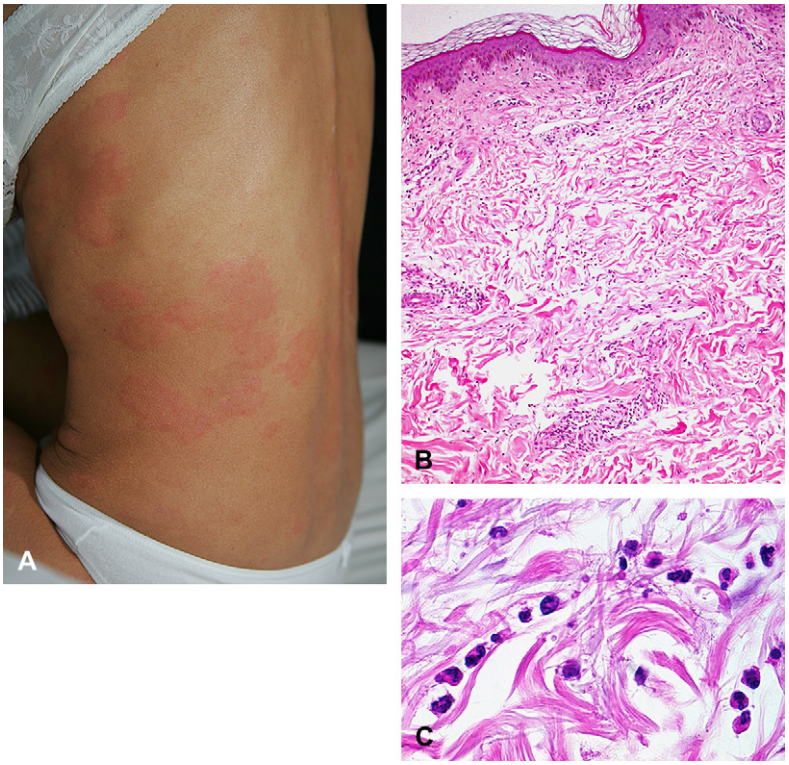

Fig 3. Chronic recurrent multifocal osteomyeleitis. **A**, Urticarial lesions on the trunk. Lesions appeared and disappeared simultaneously with fever. **B**, Mild dermal interstitial and perivascular infiltrate composed of mononuclear cells and neutrophils. **C**, Linear aggregates of neutrophils along collagen fibers. (**B** and **C**, Hematoxylin–eosin stain; original magnifications: **B**, ×100; **C**, ×1000 [oil immersion].)

or pyoderma gangrenosum–like ulcers, can be seen.[144] On histology, cutaneous lesions show a perivascular and interstitial infiltrate dominated by neutrophils, frequently with the pattern described in neutrophilic urticarial dermatosis (Fig 3, *B* and *C*); sometimes the appearance is that of a leukocytoclastic vasculitis.[144,146] In the cryopyrinopathies, urticarial skin lesions usually appear within the sixth month of life and are always associated with relevant systemic symptoms; in FMF, skin lesions are mostly erysipelas-like plaques of the lower extremities, begin in childhood or adolescence, and are simultaneously associated with systemic symptoms.[144] HIDS usually appears on the skin with erythematous macules, but also with urticarial lesions.[144] Very recently, it has been shown that the urticarial rash in cryopyrin-associated periodic syndrome (CAPS) is caused by the excessive constitutional production of IL-1β by skin mast cells.[150] A recent study on a large cohort of patients with periodic fever demonstrated that young age at onset, positive family history for periodic fever, thoracic pain, abdominal pain, diarrhea, and oral aphtosis are all independently correlated with a positive genetic test result for autoinflammatory syndromes.[151]

CONCLUSION

A variety of systemic conditions may present with urticaria-like skin lesions, which can be transient or persistent, and may be only a part of a more complex inflammatory process involving other organs and systems. The main features that can be helpful in distinguishing between common urticaria and urticarial syndromes are the long duration of individual lesions, occasional bilateral and symmetrical distribution, their resolution with hyperpigmentation or bruising, the presence of skin lesions other than wheals, and the presence of associated systemic symptoms. Differentiation between common urticaria and urticarial syndromes represents a diagnostic challenge. For these reasons, a comprehensive clinical evaluation often associated with a thorough clinicopathologic correlation is essential for diagnosis, keeping in mind that a correct interpretation by the pathologist may require a high index of suspicion by the dermatologist. In particular, even in the

presence of typical urticarial lesions, a skin biopsy specimen is helpful in confirming the diagnosis or suggesting an alternative one, particularly when lesions are unresponsive to antihistamines or when there are systemic symptoms.

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